Paget's Disease

Changes Occurring Following Treatment with Newer Hormonal Agents

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• From experience in six cases the anabolic steroid hormones, especially long-acting testosterone and estrogen preparations, are the treatment of choice in Paget's disease, as in postmenopausal osteoporosis. Details of the management of three patients over a period of four years are presented.

Roughly 4 per cent of the population, mostly persons over 40, show some evidence of Paget's disease. Only a small number of them, however, have severe manifestations requiring treatment, such as pain, bowing or fracture of the bones, pressure on nerves or heart failure. In rare cases malignant changes occur in the involved bone.

Since the cause of Paget's disease is not known, treatment in the past has been largely empirical. Reifenstein and Albright had advocated the therapeutic use of calcium, vitamin D and ascorbic acid, and, in postmenopausal women, administration of estrogens; but with fractures or immobilization, intake of calcium-containing foods, such as milk, must be restricted to avoid dangerous piling up of calcium and kidney stones, and fluids must be forced. In recent years anabolic steroid hormones, principally oral androgens and estrogens, have been employed by Gordan and others to promote bone repair, lessen bone pain and decrease urinary excretion of calcium. While these hormones probably do not arrest the disease, they seem to stabilize it and bring relief of symptoms.

More recently, Albright and Henneman demonstrated that very large doses of corticotropin (ACTH) or cortisone resulted in immediate cessation of bone pain, decrease in urinary excretion of calcium and histologic evidence of regression of the disease process. The large doses required, however, also produce dangerous side effects, such as psychosis and osteoporosis, indicating that such treatment probably should not be continued over long periods.

IT HAS BEEN ESTIMATED that roughly 3 to 4 per cent of the population over the age of 40 years has Paget's disease. A recent study by Pygott[8] of the radiologically observable incidence of this disease among some 70,000 patients examined was 3.5 per cent for both sexes over the age of 45 years, which agrees quite well with previous studies at necropsy. It appears that the incidence in men alters little from 35 to 54 years, but thereafter increases rapidly up to the age of 75; in women, by contrast, the initial incidence up to 55 years is quite similar to that of men, but the increase after 55 is not as pronounced as in men. This makes Paget's disease among the most common of nonmetabolic bone diseases. Its cause is as yet unknown. Some investigators have suggested the possibility of a primary defect in blood vessels going to bone, while others believe that the increased vascularity is a secondary effect.[14] Still others, such as McKusick,[7] have proposed a general wearing out, or "abiotrophy" of connective tissue of bone as primary cause. McKusick also cited the evidence for the known familial tendency for this disease as a genetically determined predisposing factor. In any case, it has become generally accepted, as so well described by Reifenstein and Abright,[12] that the primary event in this disorder is an accelerated, localized breakdown of bone. Areas of greatest wear and tear, such as the spine, pelvis, femur and skull, seem to have the highest degree of involvement. Depending on the healing potential, there will be repair of bone in a rather irregular fashion. In a small number of patients, decided overgrowth with deformity, bowing and fractures occur. At times pressure on vital structures, such as nerves, may produce deafness or intractable pain. If a great deal of the skeleton is involved, a greatly expanded circulatory bed through bone is produced, equivalent to multiple fistulae, and a state of high output heart failure may ensue.[9,14] In a small number of cases, sarcomatous changes take place. In Pygott's series[8] this complication was present in only 3 of 689 cases.

Since the cause of Paget's disease is unknown, treatment in the past has been largely empirical, including the use of vitamin C, vitamin D and calcium. Since many features of the initial phase of Paget's disease are similar to those of acute osteoporosis, the use of estrogen in a manner quite similar to that employed in the treatment of postmenopausal osteoporosis had been suggested by Albright and Reifenstein. This seemed to lessen the hypercalciuria and promote bone repair. In men, androgens as well as estrogens were used by Albright, as well as by others, such as Gordan[3] who

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observed that this treatment would lessen hypercalciuria, diminish bone pain and aid bone repair. More recently, Albright and Henneman[1] made the interesting observation that large doses of corticotropin (ACTH) and cortisone, contrary to expectation, would not increase or enhance the catabolic phase of Paget's disease but would actually lessen the hypercalciuria of bone catabolism, decrease the vascularity of bone and lessen bone pain. A decrease in the high cardiac output was observed in a series of patients so treated by Rapaport and co-workers.[9] This observation raises some important points as to the etiology of Paget's disease, which may represent an inflammatory or collagen-like disorder of bone. Unfortunately, however, the large doses needed to effect remission of the process would also produce undesirable side effects, such as psychosis and acute osteoporosis of the normal portion of the skeleton, so that prolonged treatment is not feasible.

The anabolic steroids, especially the more recently introduced long-acting combinations of androgens and estrogens, remain, then, in the author's experience, the most effective and practical agents in the treatment of this disease. Results of such treatment in terms of clinical improvement, chemical change and roentgenographically observable change are detailed below. The implications of some of these findings with regard to calcium needs of the adult skeleton, to the dangers of hypercalcemia, hypercalciuria and renal stone formation, and to the prevention of these hazards, are likewise discussed.

PATHOLOGIC PHYSIOLOGY

Reifenstein and Albright[12] well defined the sequence of events in Paget's disease. They also demonstrated possible ways of following the progress of the disease. It is possible to follow cycles of activity by comparing periodic x-ray films of the bones to determine whether there is decreased or increased density. One might also determine activity clinically by increased vascularity on palpation (increased warmth) or by auscultation, by the development of bone pain, or bowing or fracture. One can also gauge bone breakdown and repair on the basis of chemical changes in the blood and urine. Thus, increased bone breakdown due to whatever cause, possibly increased osteoclastic activity, will be associated with hypercalciuria, while bone repair or the increased activity of osteoblasts is reflected in increasing serum alkaline phosphatase. These indices seem to correlate quite well with clinical findings and with the x-ray appearance. A localized area of bone destruction may remain present for a long time,[13] may show radiolucency on x-ray and be accompanied by hypercalciuria during the active phase and little if any elevation of the alkaline phosphatase. With active bone repair, hypercalciuria lessens, bone density increases and the alkaline phosphatase level rises until healing is complete and a more stable state reestablished. A very high level of alkaline phosphatase is indicative of sarcomatous change. Response to treatment, likewise, can be equated in these terms, healing being signified by rise of alkaline phosphatase with decreasing urinary calcium excretion. In some instances, biopsy of specimens of bone taken serially from accessible regions, such as the skull, have well correlated with x-ray and with chemical findings.

EFFECTS OF FRACTURE AND IMMOBILIZATION

The skeleton depends for its integrity on the stresses and strains of activity. This has been well documented by the studies of Deitrick, Whedon and Shorr in immobilized normal men.[2,18] With immobilization bone breakdown continues unabated, while the processes of bone repair are halted.

What is true for normal men is even of greater importance in patients with Paget's disease because of increased bone catabolism. If such a patient is immobilized (after a fracture, for example) the accelerated bone breakdown continues, enhanced by the catabolic effect of the stress of the fracture, resulting in overloading of the circulation and renal excretory capacity for calcium. This may give rise to significant hypercalciuria, and, if fluids are not forced, and if calcium intake is not drastically restricted, kidney stones, renal calcification and finally hypercalcemia and "chemical death" may ensue.[12] Since Paget's disease commonly affects people after the age of 45, when the steroidal balance shows a greater tendency to catabolism and lessened anabolism[11] especially in postmenopausal women, immobilization becomes an even greater hazard. Similar problems are encountered in elderly, bedridden patients, in paraplegics, in patients with osteolytic malignant disease and in arthritic patients receiving cortisone, who are all subject to complications similar to those of patients who have Paget's disease. Aside from all efforts to force fluids and to reestablish mobility, the use of anabolic steroids such as the androgens and estrogens seems to be the method of choice to hasten bone repair by enhancing nitrogen and calcium retention and thus lessening the loss of these elements in the urine. Milk and its products, our most important dietary source of calcium, must be restricted until such time as a lessening of the hypercalciuria and an increase of the serum alkaline phosphatase level indicate the skeleton again can use calcium.

In general, fractures heal quite well in patients with Paget's disease, although osteoporosis may occur at sites away from the fracture.[12] On the other hand, one often observes so-called fractures, without

displacement (Figures 1 and 2) which remain virtually unchanged in appearance for prolonged periods. The roentgenograms may be those of "pseudofractures,"—perhaps blood vessel shadows, similar to the pseudofractures in osteomalacia with milkman's syndrome.[15] Patients should not be unnecessarily immobilized because of these shadows, which often remain even in well healed areas of Paget's disease.

EFFECTS AND USE OF HORMONAL AGENTS

In males, the benefits from estrogen therapy of Paget's disease as recommended by Reifenstein and Albright[12] are partially offset by the undesirable effects of such therapy, such as breast tenderness and possible testicular damage. Gordan,[3] among others, extended anabolic therapy by using sublingual methyltestosterone, in both men and women with Paget's disease, observing lessening bone pain as well as lessening of the hypercalciuria frequently observed in patients with active disease. In the present series of patients with Paget's disease in the active phase, hypercalciuria was the rule, and therefore initially reliance was put on the anabolic agents alone; vitamin D and calcium supplements were not used and milk was proscribed. This provided a means of observing the effects of treatment, or of progress of the disease, and at the same time avoided significant hypercalciuria and its inherent dangers. For good measure, ascorbic acid in doses of 500 to 1,000 mg. a day were given to improve the bone matrix. Combinations of androgens and estrogens were administered in a manner quite similar to that used in the treatment of osteoporosis in postmenopausal women.[5,6,17] In some cases in which there was clinical progress of a lesion while the patient was receiving small amounts of estrogens, both symptomatic improvement and reduction of hypercalciuria were obtained by increasing the daily dose, for example, from 1.25 to 3.5 mg. of Premarin,® or 1 to 3 mg. of stilbestrol, and the addition of methyltestosterone sublingually, or of Depo-Testosterone® 50 to 100 mg. parenterally every three to four weeks. In long term studies of three male subjects, long-acting testosterone (Delatestryl®) alone was used in two cases and a combination of long-acting testosterone and estrogen (Deladumone®) in the third. During treatment, serial determinations were made of the urine and blood calcium, phosphorus and alkaline phosphatase levels as well as clinical and x-ray observations to correlate with these changes. In the use of these hormones over four years, the effectiveness, potency and the freedom from undesirable side effects were impressive. By cyclic administration—that is, single injections every three to six weeks—treatment is greatly simplified.[6,11]

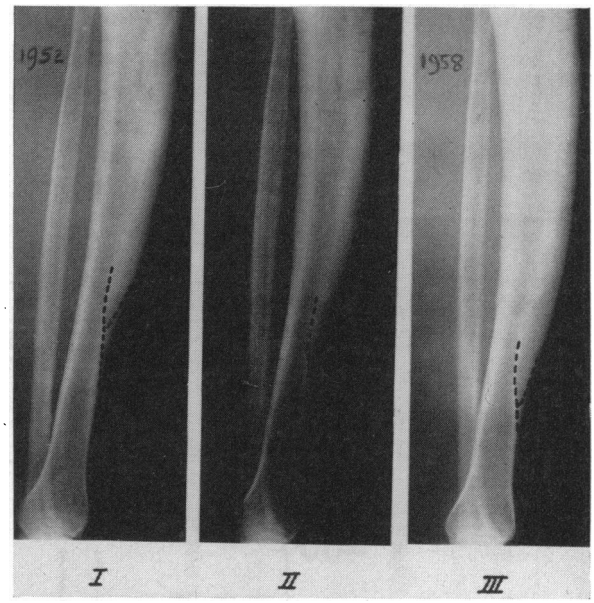


Figure 1 (Case 1).—Paget's disease of left tibia. Serial x-ray films to show progression of lesion (marked in with dotted lines). The numbers I, II and III correspond to Chart 1, showing the dates the films were taken. Note the fissures in the upper third of the tibia in all films in virtually the same location.

Cortisone was used in only one case, that of a patient with intense bone pain and progression of disease. It had to be discontinued because of the appearance of indigestion. The observations of Albright and Henneman[1] with these antianabolic agents are of greatest interest, for they seem to indicate that these agents, although not promoting bone repair, do tend to stop bone breakdown and thus cause lessening of hypercalciuria. These observers contrasted the effect of these agents with bedrest, which, as noted above, stops osteoblastic activity while bone breakdown continues unabated. Although the use of these agents—large amounts are required—is not as yet practical, there is the definite suggestion that, in contrast to the anabolic steroids which promote healing and slow down the progress of disease but do not stop it, the antianabolic agents may bring about actual cessation of the disease stimulus. The possibility of combining cortisone with anabolic agents has not, as yet, been explored. The rationale of using such combinations has been recently discussed by Reifenstein.[10]

REPORTS OF THREE CASES

CASE 1. The patient, a carpenter 54 years of age in 1952, had localized Paget's disease process in the left tibia (Figure 1, I). Except for some increased warmth, there was no complaint. The blood and urine chemical values were normal except for a

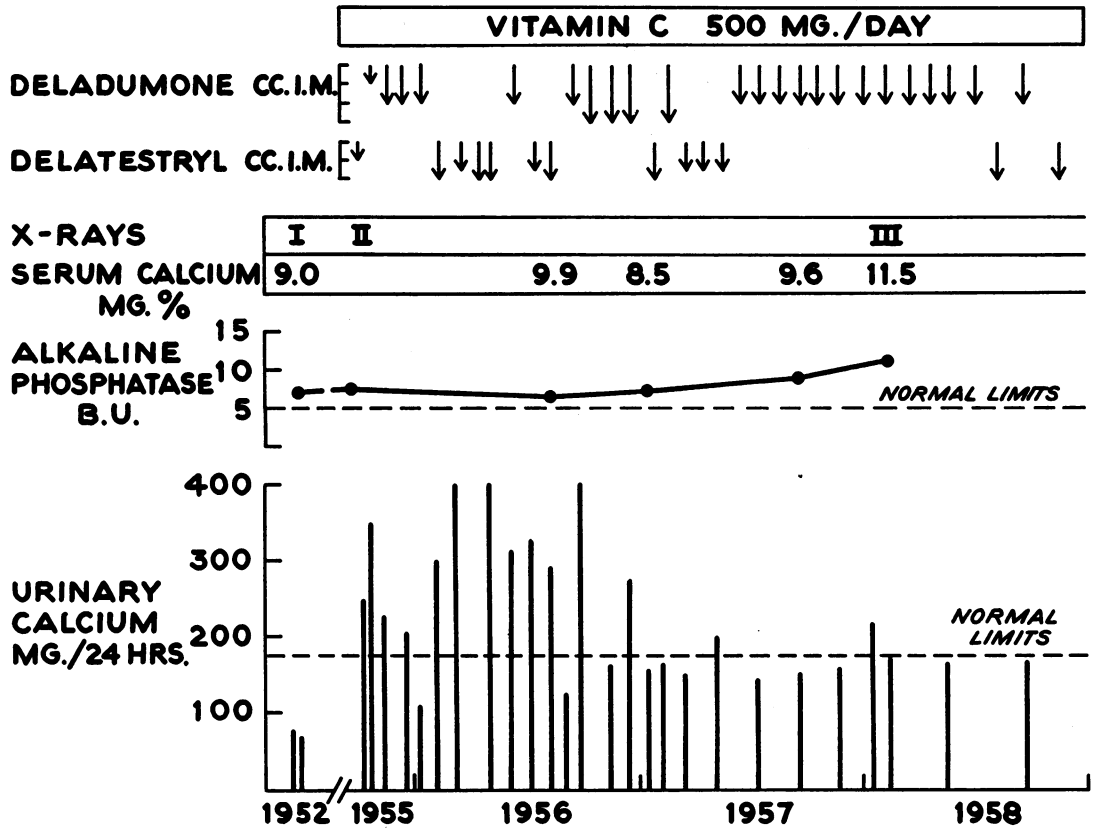
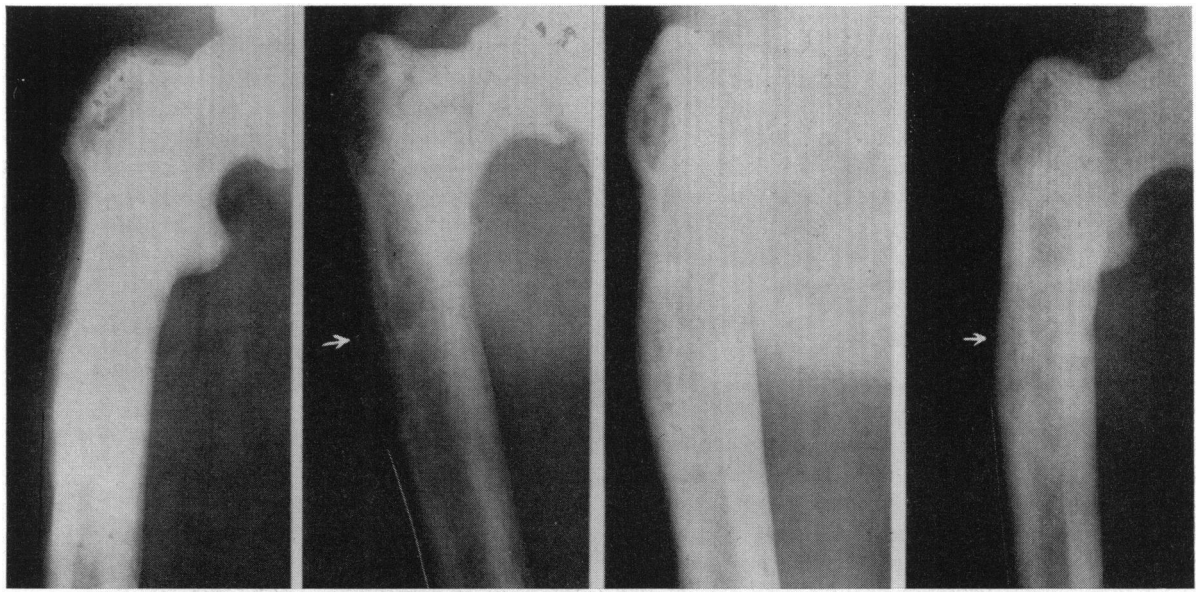


Chart 1 (Case 1).—Correlation of calcium and phosphatase levels of blood and urine while patient was being treated with Delatestryl®* and Deladumone.®†

slightly elevated alkaline phosphatase level (Chart 1). No treatment was given until 1955 when the patient returned with complaint of a great deal of pain over the shin, and some bowing. While the blood chemical values were virtually the same as in 1952, there now was intense hypercalciuria—a 4 plus reaction to a urinary Sulkowitch test and urinary calcium levels of 250 to 350 mg. per 24 hours on a diet free of milk and cheese. X-ray films (Figure 1, II) showed progression of the disease process, as well as demineralization of the tibia, with several fissure fractures in the upper third. Treatment consisted of a high protein diet, free of milk and cheese, the administration of ascorbic acid, 500 mg. daily, and long-acting anabolic hormones in the form of Delatestryl®* and Deladumone®† given in doses of 1 to 3 cc. intramuscularly every three weeks. From an inspection of Chart 1 it appears that the combined androgen-estrogen period was more effective in reducing hypercalciuria, although this is not conclusive. The patient experienced fairly prompt relief of bone pain; the hypercalciuria gradually lessened and, when calcium content approached the normal limits, two glasses of milk were allowed in the diet. There were few side effects, such as transient tenderness of the nipples, especially with Deladumone,® and no loss of libido or potency was noted in spite of some testicular atrophy. No edema was noted even when the larger doses (3 cc.*†) were given. With a lessening of hypercalciuria, the alkaline phosphatase level gradually rose. At one point in 1957, renewed pain and tenderness were noted and a short course of prednisone was tried. It had to be discontinued, however, because of indigestion. X-ray films taken in 1958 (Figure 1, III) showed definite slowing of the progressive osteoclastic lesion, with intensive recalcification of the previously osteoporotic bone. The fissure fractures noted in 1952 and 1955, however, had remained virtually unchanged in the same location.

The patient stopped hormonal treatment for reasons of his own in November 1958. He was fully active, and in May, 1959, while bowling, he slipped and fractured the tibia at the site of one of the fissures. Intense hypercalciuria with demineralization was again noted, and hormonal therapy was

*Each cc. contains 200 mg. of Delatestryl.
†Each cc. contains 90 mg. of Delatestryl and 4 mg. of Delestrogen.



October 1956 (a) | December 1956 (b) | June 1957 (c) | October 1958 (d)

Figure 2.—Serial x-ray films showing progression and healing of lesion. Note that the fissure fractures observed in 1956 (arrow) remained stationary. The area of rarefaction along the lateral margin of the femur is marked in for better visualization.

resumed. The fracture healed well with minimal immobilization.

CASE 2.* A 54-year-old laborer was first noted to have Paget's disease of the pelvis in 1951. In the absence of symptoms or chemical abnormalities except for a slightly elevated alkaline phosphatase, no treatment was given. In February 1956, a minor injury caused a fracture through a pubic ramus. X-ray films at this time showed decided progression of the disease process, with many areas of radiolucency. The alkaline phosphatase level was 13.8 Bodansky units, and the urinary calcium excretion 211 mg. per 24 hours on a diet without milk or cheese. The patient complained of a feeling of warmth and painful congestion about the left hemipelvis. Treatment was begun with a high protein diet, additional ascorbic acid, and anabolic steroid hormones, first Depo-Testosterone® and subsequently Delatestryl,® in doses of 150 to 300 mg. every three weeks. There was rapid abatement of symptoms and lessening of hypercalciuria; after a rise of the alkaline phosphatase level to 16.2 Bodansky units it gradually fell to 10.9 units over seven months of continuous treatment. The patient was fully ambulatory after a short initial period of immobilization. X-ray films in January 1957 showed remineralization of the previously observed radiolucent areas in the pelvis. Treatment was maintained at 2 cc. Delatestryl (400 mg.) every four to six weeks. The patient made no complaint of undesirable side effects.

*Studied through the courtesy of Dr. David Sutherland.

CASE 3.† A dentist 56 years of age was first observed to have Paget's disease of the upper right femur in 1956. Except for a mildly limping gait, symptoms were few. The blood and urine chemical values were normal, except for slight elevation of alkaline phosphatase content. Between July and October of 1956, x-ray films showed decided progression of the disease process. Two areas of radiolucency resembling fissure fractures appeared at the lateral margin of the upper femur (see Figure 2, a). Weight-bearing was minimized in order to lessen the danger of fracture, and treatment with anabolic steroid hormones was begun. The alkaline phosphatase level in October 1956 was 20.5 Bodansky units, and there was a 3 plus reaction to a urinary Sulkowitch test with the patient on a diet without milk or cheese. Thereupon a high protein diet, free of milk and cheese was prescribed with the addition of ascorbic acid. Delatestryl® was administered, 2 cc. every three weeks. X-ray films in December (Figure 2, b) showed further intense demineralization of the entire femur, probably due to the immobilization of the patient. At this time the alkaline phosphatase was 31.4 Bodansky units, and the urinary Sulkowitch test reaction was nil. Treatment was continued for several months, and since the patient had little pain, weight-bearing was permitted. X-ray films taken in June 1957 (Figure 2, c) showed intense recalcification of bone. Since the urinary calcium and serum

†Studied through the courtesy of Dr. Floyd H. Jergesen.

calcium levels were low, while the alkaline phosphatase level was still elevated, vitamin D 50,000 units, was added twice weekly. Receiving 2 to 3 cc. of Delatestryl®* alternating with Deladumone®† every four to six weeks, the patient continued to do well and was fully ambulatory. X-ray films in October 1958 (Figure 2, d) and later showed little bowing. The previously noted fissure fractures remained virtually unchanged. In spite of the large doses of anabolic hormones there were no side effects.

DISCUSSION

A better understanding of bone physiology, largely due to the work of Albright, has pointed the way to the need of agents to enhance bone anabolism in order to heal the lesions of Paget's disease. The anabolic steroid hormones are the best available agents to date to affect bone matrix and osteoblastic activity. They lessen hypercalciuria from increased bone breakdown, promote healing with rise of the serum alkaline phosphatase level and lessen bone pain. While they promote healing of fractures and slow the progress of the disease, they do not seem to stop it. A combination of male and female hormones, employed in a manner similar to that used in the treatment of osteoporosis, seems effective. The newer long-acting injectable hormones appear simple, convenient and effective.

Corticotropin and cortisone, in large doses, appear to stop the catabolic phase of the disease more than they interfere with bone anabolism. The large doses employed, however, act catabolically on normal bone, and also produce undesirable side effects—psychosis and indigestion—which makes prolonged treatment undesirable. Combinations of cortisone and anabolic steroids to offset some of these effects have not as yet been explored. The effects of corticotropin and cortisone may shed some light on the etiology of Paget's disease.

The lessons learned from the physiologic events of patients with Paget's disease are applicable to a variety of bone disorders. Thus, if in any situation in which there is diminished bone anabolism with continued or enhanced bone catabolism, hypercalciuria results, the treatment of primary importance is mobilization, forcing of fluids, high protein intake and, possibly the addition of anabolic hormones. The intake of calcium containing foods, such as milk, should be curtailed, in order to lessen the hypercalciuria and the likelihood of formation of renal stones, hypercalcemia and "chemical death" from calcium poisoning.[12] There seems to be far less danger from producing a dietary calcium deficiency syndrome in adult men, than there is danger from producing calcium excess. This viewpoint is even more cogent in view of recent papers, such as Hegsted's[4,16] who seriously questions whether the recommended dietary calcium intakes of adults are not too high for the needs of the skeleton. While little disadvantage has been demonstrated in people consuming much smaller amounts, examples where dietary excess may lead to aggravation of existing hypercalciuria or hypercalcemia are well known, making low calcium intakes imperative, and sometimes lifesaving. The patient with Paget's disease, in the catabolic phase, and especially when immobilized, is such an example.

*Each cc. contains 200 mg. of Delatestryl.

†Each cc. contains 90 mg. of Delatestryl and 4 mg. of Delestrogen.

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REFERENCES

1. Albright, F., and Henneman, P. H.: The suppression of Paget's disease with ACTH and cortisone, Transactions of the Assoc. of Am. Physicians, 68:238-246, 1955.

2. Deitrick, J. E., Whedon, G. D., and Shorr, E.: Effect of immobilization upon various metabolic and physiologic functions of normal men, Am. J. Med., 4:3-36, Jan. 1948.

3. Gordan, G. S.: Metabolic bone diseases in practice, osteoporosis, Paget's disease, von Recklinghausen's disease, and Albright's syndrome, Am. Practitioner and Digest of Treatment, 2:113-119, Feb. 1951.

4. Hegsted, D. M.: Calcium requirements, Nutrition Reviews, 15:257-258, Sept. 1957.

5. Henneman, P. H., and Wallach, S.: A review of the prolonged use of estrogens and androgens in postmenopausal and senile osteoporosis, A.M.A. Archives of Int. Med., 100:715-723, Nov. 1957.

6. Kolb, F. O.: Metabolic diseases of bone in the adult, Kaiser Foundation Med. Bull., 4:348-360, Sept. 1956.

7. McKusick, V. A.: Heritable Disorders of Connective Tissue, C. V. Mosby Co., St. Louis, 1956, pp. 200-205.

8. Pygott, F.: Paget's disease of bone—The radiological incidence, The Lancet, 1:1170-1171, June 8, 1957.

9. Rapaport, E., Kuida, H., Dexter, L., Henneman, P. H., and Albright, F.: The cardiac output in Paget's disease before and after treatment with cortisone, Am. J. Med., 22:252-257, Feb. 1957.

10. Reifenstein, E. C. Jr.: The rationale for the use of anabolic steroids in controlling the adverse effects of corticoid hormones upon protein and osseous tissues, So. Med. J., 49:933-960, Sept. 1956.

11. Reifenstein, E. C. Jr.: The relationships of steroid hormones to the development and the management of osteoporosis in aging people, Clin. Orthopaedics, 10:206-253, 1957.

12. Reifenstein, E. C. Jr., and Albright, F.: Paget's disease: Its pathologic physiology and the importance of this in the complications arising from fracture and immobilization, New England J. of Med., 231:343-355, Sept. 1944.

13. Seaman, W. B.: The roentgen appearance of early Paget's disease, Am. J. of Roentgenology and Radium Therapy, 66:587-594, Oct. 1951.

14. Sornberger, F., and Smedal, M. I.: The mechanism and incidence of cardiovascular changes in Paget's disease (osteitis deformans), Circulation, 6:711-726, Nov. 1952.

15. Steinbach, H. L., Kolb, F. O., and Gilfillan, R.: A mechanism of the production of pseudofractures in osteomalacia (milkman's syndrome), Radiology, 62:388-395, April 1954.

16. Walker, A. R. P.: Letter to the editor, Nutrition Reviews, 16:31, Jan. 1958.

17. Weinberg, M.: Osteoporosis: Diagnosis and treatment, J. of Am. Geriatrics Soc., 4:429-437, May, 1956.

18. Whedon, G. D., Deitrick, J. E., and Shorr, E.: Modification of the effects of immobilization upon metabolic and physiologic functions of normal men by the use of an oscillating bed, Am. J. Med., 6:684-711, June 1949.